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CLINICAL REVIEW

Untreated obstructive sleep apnea and the risk for serious long-term adverse outcomes: A systematic review

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SUMMARY

Background: Reports on the association between obstructive sleep apnea (OSA) and risk of death, cardiovascular (CV) events, diabetes and depression have been inconsistent.
Methods: We conducted a systematic review of the prognostic value of clinical and polysomnographic (PSG) characteristics of OSA for adverse long-term outcomes of untreated OSA in adult patients. A comprehensive search strategy for prognosis studies, OSA, CV events, mortality, depression and diabetes was developed in collaboration with a medical information specialist. All English language studies, from Jan 1999 to Dec 2011, with longitudinal design in adults with OSA diagnosed by PSG recording, found through Medline, Embase and bibliographies of identified articles, were considered eligible. Quality was assessed using published guidelines.
Results: Among 26 articles, ten evaluated the association of OSA with mortality, 9 with a composite CV outcome, 4 with stroke, 2 with diabetes and 1 with depression. Significant relationships between the apnea–hypopnea index (AHI) and outcomes of interest were reported in 18 studies: seven for all-cause mortality, six for composite CV events, three for stroke, one for diabetes and one for depression. The effect of AHI was attenuated by female gender, older age, absence of daytime sleepiness and higher body mass index. Due to clinical heterogeneity between studies, meta-analyses were not performed.
Conclusion: Evidence exists in men for a relationship between OSA and all-cause mortality and a composite CV outcome. Associations between OSA and other outcomes remain uncertain. Among OSA-specific markers, only AHI was a consistent predictor. Other consistent predictors were traditional CV risk factors. Research is required to identify effect modifiers and the predictive ability of various AHI threshold values and hypopnea definitions. An enhanced set of OSA-specific predictors will allow better risk stratification to guide OSA treatment.

Introduction

Obstructive sleep apnea (OSA) is a sleep-related breathing disorder characterized by repeated episodes of upper airway obstruction during sleep.[1] It affects an estimated 9% of women and 24% of men.[2,3]

There are plausible biological pathways (through chronic intermittent hypoxemia, sleep fragmentation, hemodynamic disturbances and alterations in sympathetic activity) through which untreated OSA might lead to death, cardiovascular (CV) events, diabetes or depression (Fig. 1).[4–9] However, reports on the causal relationship between OSA and such sequelae have been inconsistent.[10–23] There is also little known about which specific clinical and physiological factors best predict the occurrence of these adverse outcomes in OSA.[23] In addition, it is unknown if the thresholds for diagnosing and treating OSA should be the same in people with CV disease and those who are otherwise healthy,[23] or if the presence of OSA changes the effect of traditional risk factors for CV events and mortality. We conducted a systematic review of untreated OSA in adult patients with two goals: a) to examine the relationship between OSA and death, CV events, diabetes and

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Abbreviations

AHI	apnea–hypopnea index
BMI	body mass index
BP	blood pressure
CAD	coronary artery disease
CHF	congestive heart failure
CV	cardiovascular
CVD	cardiovascular disease
DS	daytime sleepiness
HR	hazard ratio
HTN	hypertension
IHD	ischemic heart disease
MI	myocardial infarction
OHS	obesity-hypoventilation syndrome
OR	odds ratio
OSA	obstructive sleep apnea
PSG	polysomnographic
RDI	respiratory disturbance index
RR	relative risk
SaO_2	oxygen saturation
SHHS	Sleep Heart Health Study
TST	total sleep time
WSCS	Wisconsin Sleep Cohort Study

depression; and b) to determine the prognostic value of demographic, clinical and polysomnographic (PSG) characteristics of OSA on these long-term outcomes. Non-disease outcomes such as motor vehicle or occupational accidents, although important, were not examined in the current review.

Methods

Data sources and searches

In collaboration with disease experts and a medical information specialist, we developed a comprehensive search strategy for prognostic studies of OSA with outcomes of myocardial infarction (MI), stroke, mortality, depression and diabetes.[24] All English language peer-reviewed studies published from Jan 1999 to Dec 2011 with prospective or retrospective data collection and a longitudinal design,[25] found through Medline, Embase and bibliographies of identified articles and reviews, were considered eligible. Basic search terms used are presented in Table S1.

Inclusion criteria

We included studies that targeted adult patients with a diagnosis of OSA on the basis of the apnea–hypopnea index (AHI) made by PSG recording and followed them for at least one year. We excluded studies without an untreated OSA group or where more than 50% of participants were pregnant or had previous CV events or other severe neurological or psychiatric diseases. For more details see Appendix A.

The serious adverse outcomes (either objectively documented or self-reported) considered were: CV events, both non-fatal and fatal; all-cause mortality; diabetes; and depression. All available clinical and PSG variables were treated as potential predictors; however we report on only those with a statistically significantly association with our outcomes in at least one study. Predictors were collated into four domains: patient demographic characteristics, medical history, physical exam findings, and OSA characteristics (clinical symptoms, PSG indexes, treatment options).

Study selection

Two independent reviewers (TK, TM) assessed study titles and abstracts. If the title or abstract suggested that the study might meet the inclusion criteria, both reviewers assessed the full article. Differences of opinion were resolved by discussion. A third reviewer (GT) was consulted where consensus could not be reached.

Data extraction and quality assessment

Study quality was assessed independently by two reviewers (TK, TM) using guidelines developed by Hayden et al., for assessing prognostic studies.[26] The appraisal had two steps. The first step assessed the items related to six potential sources of bias (study participation and attrition; prognostic factor and outcome measurements; confounding measurement and account; and analyses). The second step judged presence of potential biases as “Yes”, “Partly”, “No”, or “Unsure”. For studies with sufficiently high quality, we abstracted data on the relationships between our outcomes and both clinical information and PSG indices.

To summarize the level of evidence, we used a system similar to the Scottish Intercollegiate Guidelines Network (SIGN) methodology[27]: i) “++” when all or most of the quality criteria proposed by Hayden et al. were fulfilled (allowing one “Partly” while appraising all potential sources of bias); ii) “+” when some of the

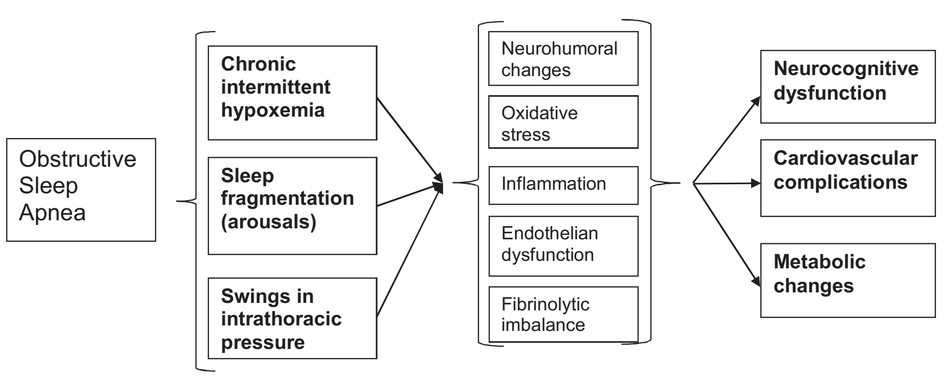

Fig. 1. The long-term consequences of untreated obstructive sleep apnea (OSA): possible links (modified from Tasali and Ip (2008)), Bradley and Floras (2009), Knoepke and Aloia (2009), Bagai (2010) and Sharma and Kavuru (2010).

criteria were fulfilled; iii) "−" when few or no criteria fulfilled (at least one "Yes"). Additionally, as proposed by SIGN, studies with retrospective data collection did not receive a "++" rating, as this design is weaker than prospective data collection. Below, we refer to group i) as 'high quality studies' and group ii) as 'moderate quality studies'.

Data synthesis and analysis

The degree of clinical heterogeneity between studies ruled out meta-analyses. Findings for studies with sufficient quality were synthesized through tabulation and qualitative description. Only brief summary results are provided for studies that did not meet quality criteria.

Results

Literature search and quality assessment

Of 2547 articles identified, 49 were selected for full-text review and 32 were included (Fig. 2). Supplementary Table S2 shows reasons for exclusion of 17 studies.

Of the 32 studies (Table 1), 26 were assessed as having "Partly" or "No" on all bias criteria and were included in our main analyses.

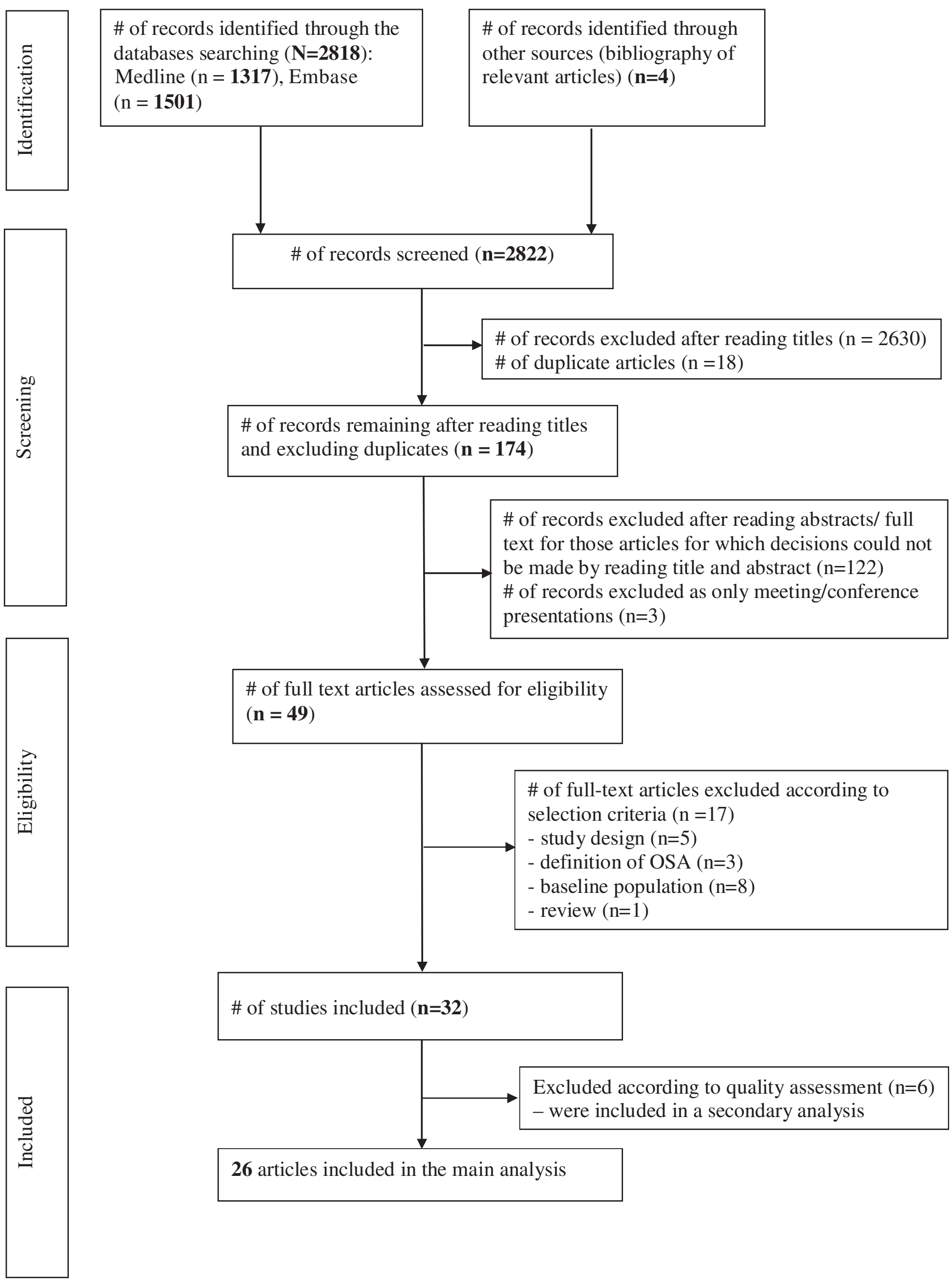

Fig. 2. Flow diagram for identification of relevant studies (from Jan 1999 to Dec 2011).

Table 1
Quality assessment of studies using guidelines developed by Hayden et al., 2006.

	Study	Study participation	Study attrition	Prognostic factor	Outcome	Confounding measurement and account	Analysis	Overall assessment of the study
1.	Ambrosetti et al., 2006	Partly	Partly	No	Unsure[b]	Yes[a]	Partly	–
2.	Ancoli-Israel et al., 2003	Partly	No	Yes[c]	No	No	No	–
3.	Arzt et al., 2005	No	No	No	Partly	Partly	No	+
4.	Buchner et al., 2007	No	No	No	No	Partly	Partly	+
5.	Campos-Rodriguez et al., 2005	No	Partly	Partly	Partly	No	No	+
6.	Celen et al., 2010	Partly	Partly	No	Partly	Partly	Yes[d]	–
7.	Chami et al., 2011	No	No	No	No	Partly	No	++
8.	Cordero-Guevara et al., 2011	No	Partly	No	Partly	No	No	+
9.	Doherty et al., 2005	No	Partly	Partly	No	Partly	Partly	+
10.	Fisher et al., 2002	Partly	Partly	No	No	Yes[a]	Yes[d]	–
11.	Gooneratne et al., 2011	No	Partly	Partly	No	Partly	No	+
12.	Gottlieb et al., 2010	No	No	No	No	Partly	No	++
13.	Hader et al., 2006	Partly	Partly	Partly	Partly	Yes[a]	Yes[d]	–
14.	Johansson et al., 2011	Partly	No	No	No	Yes[a]	Yes[d]	–
15.	Lavie et al., 2009	No	No	No	No	Partly	No	+ (due to RD)
16.	Lavie et al., 2007	No	Partly	Partly	No	Partly	Partly	+
17.	Lavie et al., 2005	No	No	No	No	No	No	+ (due to RD)
18.	Marin et al., 2005	No	No	Partly	No	Partly	Partly	+
19.	Marshall et al., 2009	No	No	Partly	Partly	Partly	Partly	+
20.	Marshall et al., 2008	No	No	Partly	No	Partly	No	+
21.	Marti et al., 2002	No	No	Partly	No	Partly	Partly	+
22.	Munoz et al., 2006	No	No	Partly	No	Partly	No	+
23.	Nakamura et al., 2009	No	No	Partly	No	No	No	+ (due to RD)
24.	Peker et al., 2006	No	No	Partly	No	Partly	Partly	+
25.	Peker et al., 2002	No	No	Partly	No	Partly	Partly	+
26.	Peppard et al., 2006	No	No	Partly	Partly	Partly	No	+
27.	Punjabi et al., 2009	No	No	No	No	Partly	No	++
28.	Redline et al., 2010	No	No	No	No	Partly	No	++
29.	Reichmuth et al., 2005	No	No	No	No	Partly	No	++
30.	Shah et al., 2010	No	No	No	No	Partly	No	+ (due to RD)
31.	Yaggi et al., 2005	No	No	No	No	Partly	No	+ (due to RD)
32.	Young et al., 2008	No	No	No	No	No	No	++

RD – retrospective design.
[a] A study does not address the possibility of confounding (for Johansson study (2011) – was addressed only for patients with cardiovascular disease at baseline).
[b] Outcomes and the criteria used for measuring them are not clearly defined.
[c] Obstructive sleep apnea (OSA) was not separately reported from central sleep apnea (CSA) as a predictor.
[d] Not appropriate analyses were used.

Six of these studies, carried out under the auspices of the Sleep Heart Health Study (SHHS) or Wisconsin Sleep Cohort, were high quality studies ("++"). Among the remaining 20 studies, five fulfilled most of the criteria but were penalized by the SIGN criteria for being retrospective cohort studies.

Study characteristics

Supplementary Table S3 shows summaries of the included studies: population characteristics, definitions of OSA, follow-up time, outcome and analyses.

Fourteen studies were based on clinical populations and 12 on community samples. Follow-up time varied from 2.8 years[35] to 13.8 years[14,26] with average follow-up time of 7.1 years. The mean age ranged from 47[15] to 78 years,[28] with an average of 58 years. Four of 14 studies based on clinical samples included only males; in the others, men represented from 72.3% to 90.2% of samples. In 12 community-based studies, men comprised between 28.1%[28] and 74.6%[10,21] of subjects.

The majority of studies (19 of 26) used full standard PSG recording to diagnose OSA. Considerable between-study variation was observed in PSG recording systems and the definitions of PSG indexes, particularly AHI (Table S3). Thresholds for diagnosing OSA varied: AHI $\geq$ five events/h (18 studies)[10,12,14–16,18–22,28–35]; AHI $\geq$ 10 events/h (5 studies)[36–40]; AHI $>$ 15 events/h (one study)[41]; and $\geq$ 30 events/h overnight sleep-related obstructive events (2 studies).[42,43] Most studies (19 of 26) defined apnea as a complete cessation of airflow for at least 10 s.[12,14–16,18–20,22,28–

Table 2
Number of supporting studies of patient clinical characteristics and polysomnographic (PSG) indexes reported to prognosticate outcome of interest.

	Total	Outcome				
		Mortality	CV events[a]	Stroke[b]	Diabetes	Depression
Study, total number	26	10	9	4	2	1
Demographics						
Age	14/23	7/8	5/8	2/4	0/2	0/1
Sex	4/18	2/7	1/5	1/3	0/2	0/1
Race	1/8	1/2	0/4	0/2	–	–
History at baseline						
CV comorbidities	8/18	4/8	3/6	1/2	0/1	0/1
Pulmonary disease	4/9	4/6	0/3	–	–	–
Diabetes	6/20	3/8	2/8	1/3	–	0/1
Smoking status	4/22	1/7	2/9	1/3	0/2	0/1
Clinical exam						
BMI	3/24	3/10	0/8	0/4	0/1	0/1
Blood pressure	5/21	2/7	2/9	0/3	1/1	0/1
Disease characteristics						
AHI or equivalent	18/26	7/10	6/9	3/4	1/2	1/1
Ox desaturation	3/7	1/4	1/1	1/2	–	–
Arousal index	1/2	0/1	–	1/1	–	–
Sleep duration	1/1	1/1	–	–	–	–
OSA treatment	7/10	2/3	5/6	–	0/1	–
Time since baseline	1/1	–	1/1	–	–	–

AHI - apnea-hypopnea index; BMI - body mass index; CV - cardiovascular; OSA - obstructive sleep apnea; Ox - oxygen.
First number: was reported as a significant predictor; second number: was included in statistical model. "–" was not included in a model.
[a] Fatal or non-fatal, including composite outcomes.
[b] Including one study with composite outcome: stroke or death from any cause.

[33,36–41] By contrast, the definition of hypopnea was highly variable. One criterion was a decrease in airflow from the preceding baseline level: eight studies required only a clearly discernible decrease.[12,14–16,18,20,22,28] Others required a decrease of at least 30% (three studies),[19,32,33] 50% (nine studies)[29–31,36–41] or 70% (one study)[34] and lasting for at least 10 s. A second criterion, which is currently recommended by the American Academy of Sleep Medicine,[44] that the decrease be associated with signs of

Table 3
The most common significant predictors reported.

Study, author and year	AHI	CV comorbidities	Age	Sex	BMI	BP	Diabetes	Treatment	Smoking
Mortality									
Clinical sample									
Campos-Rodriguez F. et al., 2005	○	●	●	○	○	●	○	⦿	○
Lavie P. et al., 2005	●	—	⦿	Men	●	—	—	—	—
Lavie P. et al., 2007	○	●	Strat	Men	●	○	●	—	○
Lavie P. et al., 2009	○	●	●	○	○	—	●	—	—
Marti S. et al., 2002	●	○	● >60 y	○	○	○	○	⦿	○
Nakamura H. et al., 2009	●	—	●	●	⦿	—	—	No CPAP	—
Population based sample									
Gooneratne N.S. et al., 2011	●(EDS+/SDB+)	●	●	●	○	○	○	—	○
Marshall NS. et al., 2008	●	○	●U	○	○	●U	●U	—	●U
Punjabi NM. et al., 2009 a) men	●	○	Strat	Men	○	○	○	○	○
Punjabi NM. et al., 2009 b) women[a]	○	○	Strat	Women	○	○	○	○	○
Young T. et al., 2008	●	○	○	○	○	○	○	Excluded	○
Non-fatal and fatal cardiovascular events									
Clinical sample									
Buchner NJ. et al., 2007	Untreated OSA – reference gr.	○	○	○	○	○	○	⦿	○
Cordero-Guevara et al., 2011	○	●	●	⦿Women	○	○	●	⦿	○
Doherty LS. et al., 2005	○	●	○	92% Men	○	○	●	⦿	○
Marin JM. et al., 2005 a) fatal	●	●	●	Men	Matched	○	○	○	○
Marin JM. et al., 2005 b) non-fatal	●	●	●	Men	Matched	●	○	○	●
Peker Y. et al., 2002	●	Excluded	●	Men	○	○	Excluded	⦿	○
Peker Y. et al., 2006	●	Excluded	●	○	○	●	○	⦿	○
Shah NA et al., 2010	●	○	●	○	○	○	○	—	●
Population based sample									
Chami HA. et al., 2011	● change in AHI	—	○	○	○	○	○	—	○
Gottlieb D. et al., 2010 a) men	● in HF ● in CHD, ≤70	○	Strat	Men	○	○	○	—	○
Gottlieb D. et al., 2010 b) women[a]	○	○	Strat	Women	○	○	○	—	○
Stroke or death from any cause									
Clinical sample									
Yaggi et al., 2005	●	○	●	○	○	○	○	—	○
Stroke									
Population based sample									
Arzt M. et al., 2005[a]	○	—	○	○	○	—	—	—	—
Munoz R. et al., 2006	●	Excluded	○U	●U	○U	○U	○U	Excluded	○U
Redline S. et al., 2010 a) men	●	○	●	Men	○	○	○	Excluded	○
Redline S. et al., 2010 b) women	○	●	●	Women	○	○	●	Excluded	●
Diabetes									
Population based sample									
Marshall NS. et al., 2009	●	○	○	○	○	●U	○	—	○
Reichmuth KJ. et al., 2005[a]	○	—	○	○	—	—	—	○	○
Depression									
Population based sample									
Peppard et al., 2006	●	○	○	○	○	○	○	Excluded	○

AHI – apnea–hypopnea index; BMI – body mass index; BP – blood pressure; CHD - chronic heart disease; CV – cardiovascular; EDS - excessive daytime sleepiness; gr. - group; HF - heart failure; OSA - obstructive sleep apnea; SDB - sleep disordered breathing; Strat – stratification was performed; U – univariate
In gray – studies that met most of the quality criteria. Men – only men in the sample; Women – only women in the sample.
● – positive significant association; ⦿ – negative significant association; ○ – no significant association was reported in multivariable model; "—" – was not included in the model.
[a] No correlation was reported in fully adjusted model between OSA and outcomes of interest.

Table 4
Direction, magnitude, and statistical significance of associations reported between the most common significant predictors and adverse long-term outcomes.[a]

#	Study	AHI/RDI	CV comorbidities at baseline	Age	Sex
Mortality					
Clinical sample					
1.	Campos-Rodriguez F. et al., 2005	AHI, events/h OR U = 0.99 (0.98–1.00)	Arterial HTN OR = 3.25 (1.24–8.54)	OR = 1.06 (1.01–1.10)	Women OR U = 1.44 (0.64–3.24)
2.	Lavie P. et al., 2005	RDI 31-40: HR = 2.18 (1.33–3.57); RDI > 40: HR = 2.49 (1.59–3.89)	–	For RDI > 50, negative Trend for age ($p < 0.04$), RR = NS	Only men
3.	Lavie P. et al., 2007	RDI, events/h OR = 1.02 (0.90–1.15)	CHF OR = 5.47 (1.06–28.31)	NS	Only men
4.	Lavie P. et al., 2009	RDI, events/h HR = 1.01 (1.0–1.02)	MI: HR = 3.82 (1.88–7.75) IHD: HR = 2.30 (1.33–3.99) Stroke: HR = 2.70 (1.22–5.99) HL: HR = 0.38 (0.19–0.76)	HR = 1.09 (1.05–1.13)	Men: HR = 1.05 (0.63–1.74)
5.	Marti S. et al., 2002	AHI, events/h HR = 0.71 (0.33–1.50)	HTN: HR = 1.05 (0.57–1.93) CHD: HR = 1.31 (0.50–3.40)	50–60 y: HR = 1.54 (0.73–3.24) >60 y: HR = 3.20 (1.48–6.92)	Men: HR = 1.51 (0.63–3.60)
6.	Nakamura H. et al., 2009	AHI, events/h HR = 1.01 (1.01–1.021)	–	HR = 1.08 (1.06–1.11)	Men: HR = 2.01 (1.1–3.69)
Population based sample					
7.	Gooneratne N.S. et al., 2011	EDS+/SDB+ (AHI ≥ 20 events/h) : HR = 2.28 (1.46–3.57)	Angina: HR = 1.67 (1.12–2.50)	HR = 1.09 (1.06–1.12)	Men: HR = 1.53 (1.08–2.17)
8.	Marshall NS. et al., 2008	Per ten units of RDI: HR = 1.72 (1.13–2.62) RDI ≥ 15/h: HR = 6.24 (2.01–19.39) 5 – <15: HR = 0.47 (0.17, 1.29)	Angina: HR U = 1.91 (0.67-5.44)	Per decade: HR = 3.58 (1.97–6.52)	Men: HR U = 1.68 (0.69–4.07)
9.	Punjabi NM. et al., 2009	AHI ≥ 30.0 (entire sample): HR = 1.46 (1.14–1.85); AHI in men: 15–29.9: HR = 1.27 (1.00–1.65) ≥30.0, HR = 1.54 (1.15–2.08) AHI (≥30.0) in men ≤ 70 y: HR = 2.09 (1.31–3.33) CAD related death: AHI ≥ 15 in men, HR = 1.69 (1.13–2.52)	NS	Stratification by age	Stratification by sex
10.	Young T. et al., 2008	AHI ≥ 30, HR = 2.7 (1.3–5.7) AHI ≥ 30, untreated: HR for all-cause mortality = 3.8 (1.6–9.0); HR for CV mortality = 5.2 (1.4–19.2). HR, all-cause mortality, free of diagnosed stroke and CVD at baseline = 3.2 (1.4–7.1)	NS		
Non-fatal and fatal cardiovascular events					
Clinical sample					
11.	Buchner NJ. et al., 2007	Untreated OSA – reference gr.	NS		
12.	Cordero-Guevara et al., 2011	AHI, events/h RR = 1.0 (0.99–1.01)	CV events RR = 6.25 (3.79–10.31)	RR = 1.06 (1.03–1.08)	Women RR = 0.25 (0.09–0.76)
13.	Doherty LS. et al., 2005	AHI (15–35; 35–55; 55.3–131.5); p un = 0.09, HR (NS)	IHD: HR = 8.61 (1.76–42.02)	Age (13–47; 47–56; 56–77), p un = 0.46	92% men
14.	Marin JM. et al., 2005	Untreated severe OSAH (AHI > 30): For CV death, OR = 2.87 (1.17–7.51); For non-fatal CV events, OR = 3.17 (1.12–7.52).	CVD For CV death: OR = 2.54 (1.31–4.99); For non-fatal CV events: OR = 1.77 (1.03–3.09)	For CV death: OR = 1.09 (1.04–1.12); For non-fatal CV events: OR = 1.09 (1.05–1.13)	Only men
15.	Peker Y. et al., 2002	OSA (ODI ≥ 30): OR = 4.9 (1.8–13.6)	Excluded	OR = 23.4 (2.7–197.5)	Only men
16.	Peker Y. et al., 2006	OSA (ODI ≥ 30): RR = 4.6 (1.83–11.6)	Excluded	RR: 1.06 (1.02–1.11)	NS
17.	Shah NA et al., 2010	AHI ≥ 5: HR = 2.06 (1.10–3.86) 5–14: HR = 2.22 (1.10–4.45) 15–29: HR = 2.65 (1.27–5.56) ≥30: HR = 2.82 (1.46–5.45)	HTN: HR = 1.43 (0.88–2.32) A fib: HR = 0.83 (0.37–1.83)	HR = 1.07 (1.05–1.10)	Men: HR = 1.30 (0.77–2.21)
Population based sample					
18.	Chami HA. et al., 2011	For AHI change being in one higher ordinal level (↑ in AHI > 15; ↑ in AHI by 5–15; stable AHI (−4.9 to 4.9); ↓ in AHI by 5–15, ↓ in AHI > 15: OR = 1.65 (1.11–2.43)	—	NS	
19.	Gottlieb D. et al., 2010	CHD, for men ≤ 70 y, per 10-unit increase in AHI: HR = 1.10 (1.00–1.21); AHI ≥ 30, HR = 1.68 (1.02–2.76) HF for men, HR = 1.13 (1.02–1.26); AHI ≥ 30, HR = 1.58 (0.93–2.66)	NS	Stratification by age	Stratification by sex

Table 4 (*continued*)

#	Study	AHI/RDI	CV comorbidities at baseline	Age	Sex
Stroke or death from any cause					
Clinical sample					
20.	Yaggi et al., 2005	AHI ≥ 5: HR = 1.97 (1.12–3.48) AHI > 36: HR = 3.30 (1.74–6.26)	A fib: HR = 0.91 (0.45–1.86) HTN: HR = 1.19 (0.75–1.90)	HR = 1.08 (1.06–1.11)	Men: 0.78 (0.48–1.28)
Stroke					
Population based sample					
21.	Arzt M. et al., 2005	AHI: ≥5 to <20, OR = 0.29 (0.04–2.36); ≥20, OR = 3.08 (0.74–12.81)	—	NS	
22.	Munoz R. et al., 2006	AHI ≥ 30 vs AHI 0–29: HR = 2.52 (1.04–6.10)	Excluded	Age, years, *p U* = 0.204, HR (NS)	Men: U, *p* = 0.010 HR (NS)
23.	Redline S. et al., 2010	AHI > 19 in men: HR = 2.86 (1.10–7.39)	Women, HTN medication use: HR = 1.94 (1.25–3.05)	Men, HR (NS); Women, HR per 10 y = 2.77; 2.12–3.61	Stratified by sex
Diabetes					
Population based sample					
24.	Marshall NS. et al., 2009	Moderate-to-severe SA (≥15 RDI), OR = 13.45 (1.59–114.11)	Angina, OR *U* = 1.74 (0.21–n14.62)	Age, per decade, OR *U* = 1.29 (0.53–3.13)	Male, OR *U* = 3.19 (0.39–25.9)
25.	Reichmuth KJ. et al., 2005	AHI 5–15: OR = 1.56 (0.80–3.02) AHI > 15: OR = 1.62 (0.67–3.65)	—	NS	
Depression					
Population based sample					
26.	Peppard et al., 2006	Increase to the next higher category (0 < AHI < 5, 5 ≤ AHI < 15, AHI ≥ 15): OR = 1.8 (1.3–2.6)	NS		

AHI – apnea–hypopnea index; A fib – atrial fibrillation; AP – arterial pressure; CHD – coronary heart disease; CHF – congestive heart failure; CV - cardiovascular; EDS – excessive daytime sleepiness; HL – hyperlipidemia; HR – hazard ratio; HTN – hypertension; IHD – ischemic heart disease; MI – myocardial infarction; NS – non specify; ODI – oxygen desaturation index; OR – odds ratio; OSA – obstructive sleep apnea; RDI – respiratory disturbance index; RR – relative risk; SDB – sleep disordered breathing; UAP – upper airway problems; U – univariate.

[a] Only results from the multivariable analysis were reported. Univariate associations were reported only in a case when adjustment was not performed. Where possible, 95% confidence intervals were reported.

physiological arousal or a drop in oxygen saturation (SaO_2), also varied between studies.

All statistically significant predictors of our outcomes are reported in Table 2.

Overall predictors of all outcomes [summary]

The 26 studies identified 15 factors that were statistically significantly associated with one or more outcomes in OSA patients (Table 2). The most reproducible (reported in three or more studies) statistically significant predictors were[1]: OSA-related (AHI, significant in 18 of 26 that reported it; SaO_2, significant in 3/7; and OSA treatment, significant in 7/10)[2]; demographic characteristics (age, significant in 14/23 and sex, significant in 4/18)[3]; history at baseline (CV comorbidities, significant in 8/18, diabetes, significant in 6/20, pulmonary disease significant in 4/9 and smoking status, significant in 4/22); and[4] physical exam (blood pressure (BP), significant in 5/21, and body mass index (BMI) significant in 3/24).

Important predictors of each outcome

Tables 3 and 4 show results for the predictors most frequently found to have significant associations. Ten studies evaluated the association of OSA with mortality, 9 with a composite CV outcome, 4 with stroke, 2 with diabetes and 1 with depression.

Mortality: A statistically significant association with mortality was found in three or more studies for each of the following five predictors: AHI, CV comorbidities, pulmonary disease, diabetes and age at baseline (Table 3). Of two high quality studies, one found no significant association between OSA and mortality for women in a fully adjusted model.[32]

CV events: An association with CV events was found in three or more studies for each of four predictors: AHI, CV comorbidities, age at baseline, and treatment for OSA (Table 3). One of two high quality studies found no association between OSA and CV events for women in a fully adjusted model.[12] We observed diversity in the definitions of fatal and non-fatal individual CV events. Fatal CV events included the following in different combinations: any CV related cause of death, death from myocardial infarction (MI), stroke, ischemic heart disease (IHD), cardiac dysrhythmias, cardiomyopathy, cerebrovascular disease or atherosclerosis.[14,30,33,35,41] Non-fatal CV events included the following in different combinations: hypertension (HTN), coronary artery disease, cardiac arrhythmias, congestive heart failure (CHF), atherosclerosis or cerebrovascular disease including stroke.[14,30,33–35,41,43]

Stroke: A predictive association with stroke was found in three of four studies only for AHI at baseline. Of three medium quality studies, one study found no association between OSA and stroke in a fully adjusted model.[15] One high quality study found an association between AHI and stroke in men but not in women.[18]

There was little evidence of an association between OSA and incident diabetes or depression. Of two high quality studies, one did not find a relationship between OSA and diabetes in a fully adjusted model.[20] One moderate quality study reported an association between OSA and depression.[22]

Sleep-apnea related predictors

Among OSA-specific markers, only AHI was a consistent predictor. Other consistent predictors were those traditionally included in models predicting risk of CV events in general populations (CV comorbidities, diabetes, BMI, BP and smoking status at baseline, age and sex).

Eighteen studies reported statistically significant associations between AHI and outcomes of interest, with a higher AHI predicting increased risk of an adverse event (Table 4). However, when AHI was categorized, the predictive thresholds differed from study to

study. In one study a relationship was shown between incident cardiovascular disease (CVD) and change in AHI over 5 years.[34]

Several variables appear to modify the effect of AHI on our outcomes: sex, age, BMI and presence of excessive daytime sleepiness (DS).

Analyses stratified by sex were performed in three of the six high quality studies. Only men showed a significant positive association in adjusted models between AHI and ischemic stroke,[18] mortality[32] or incident CV events.[12] In the latter two studies, a significant interaction between sex and AHI was found.[12,18]

A number of high and moderate quality studies have shown an attenuation of risk with increasing age. In a study performed by Lavie et al., even in very severe OSA (AHI $>$ 50), only men younger than 50 showed excess all-cause mortality in comparison with the general population.[37] Later studies (2007, 2009) by the same group found different predictors in those below and above age 62,[38] and showed that an elderly sample with moderate OSA had significantly lower mortality rates than a matched population cohort.[39] The SHHS also found a significant interaction between AHI and age, with increased risk of mortality for AHI $\geq$30 events/h (vs. AHI $<$ 5 events/h) in men aged 40–70 y (hazard ratio (HR): 2.1; 95% CI: 1.3–3.3) but not in older men.[32] The SHHS later reported similar results when after adjustment for multiple risk factors, a significant association between a 10-unit increase in AHI and incident CHD was found only for men 40–70 years of age (HR: 1.10; 95% CI: 1.00–1.21); however, the interaction between AHI and age was not statistically significant.[12] Complicating matters still further, Gooneratne et al., found a significant association between OSA and mortality in older adults (age $>$ 65 y) only in the presence of symptoms of excessive DS.[28]

There is conflicting evidence on the role of obesity. Lavie et al., found a significant interaction between BMI and AHI and concluded that OSA affects all-cause mortality by interacting with obesity, but not independently.[38] Another study that looked at an interaction between AHI and BMI found that the hazard rate for mortality associated with an AHI of 5–29 events/h was significantly lower among patients with BMI of $\geq$30 kg/m^2 than in those with a BMI below 25 kg/m^2 (HR: 0.21; 95% CI: 0.05–0.92).[31]

The predictive ability of sleep-related hypoxemia was tested only in seven studies and was reported to be significantly associated with outcomes of interest in three of them. As with AHI, sex and age modified the effect of SaO_2 on our outcomes. One study of high quality found the percentage of total sleep time with oxyhemoglobin saturation below 90% (TST90) is independently associated with mortality,[32] however, only for men $<$70 years old but not for older men or women of both age categories. Compared to men in the first three quartiles of TST90, men in the fourth quartile (TST90 $>$ 2.70%) had an adjusted HR of 1.83 (95% CI: 1.31–2.52) for mortality.[32] Furthermore, SaO_2 was found significantly associated with coronary artery disease (CAD) (relative risk (RR):1.11 (95% CI: 1.02–1.22))[43] and stroke (HR:1.78 (95%CI: 1.01–3.15)).[18] However, for stroke, this association was reported only for women, and only the second tertile of the percentage of sleep time with SaO_2 less than 90% (0.23–1.95) was significantly associated with incident ischemic stroke in a fully adjusted model.[18]

There was minimal and inconsistent evidence to support an independent relationship between our outcomes and other PSG indexes (arousal index, sleep duration), or other demographic and clinical characteristics (presence of snoring, race, history of pulmonary disease or cancer at baseline, left ventricular ejection fraction).

Discussion

We conducted a systematic review in order to investigate the relationship between OSA and death, CV events, diabetes and depression and determine the prognostic value of demographic, clinical and PSG characteristics of OSA on these outcomes. Of 32 articles evaluated, 26 at least partly addressed sources of potential study biases. All six studies classified as 'high quality' were based on two large seminal community-based cohort studies designed to evaluate the long-term consequences of OSA: the Wisconsin Sleep Cohort Study (WSCS) and the Sleep Heart Health Study (SHHS). None of the studies based on clinical samples was deemed 'high quality'. Both large sleep cohorts and other smaller community and clinical based studies showed that among men OSA is an independent risk factor for death from all-causes and for a composite CV outcome. We did not find clear evidence of those associations among women, or between OSA and individual CV outcomes, diabetes and depression.

Despite cross-sectional studies having shown that OSA is associated with diabetes or its early markers,[20,45,46] there is little published evidence of a longitudinal association between OSA and diabetes. Of the two studies assessing this association, the one high quality study[20] found a non-significant association between these two conditions after adjustment for age, sex, and body habitus. The other found a significant association between moderate-severe OSA and incident diabetes compared to subjects without OSA. However, only nine incident cases of diabetes were observed within 4 y.[21] This inconsistency across studies and designs could be explained by variability in the definition of diabetes, combining type I and II diabetes (e.g., in administrative datasets), common pathogenetic risk factors (e.g., obesity) for both diseases, and the long time required for developing and diagnosing these conditions.

There is a lack of evidence for a longitudinal association between OSA and depression. Only one study of moderate quality reported such an association.[22] The paucity of good quality longitudinal studies of OSA and depression may be explained by the following factors: challenges in establishing a diagnosis of depression; differences in sensitivity and specificity of the screening or diagnostic tool chosen; a lack of a validated algorithm to define depression from administrative data; and differences in prevalence of hospitalized depression and depression diagnosed by the primary care physician.[47–49]

The dearth of published evidence on associations between OSA and individual CV outcomes could mean there are few true relationships. The small numbers of events per separate component of the composite CV outcomes and the variety of definitions for these components limited the conclusions that we could draw.

Identifying a causal role of OSA in developing CV events is difficult since all the conditions are chronic, have long latent periods before symptoms appear, and have multifactorial and overlapping origins, sharing common risk factors such as sex, being overweight and smoking.[4,5,23,50] Perhaps this is one reason that OSA has been largely overlooked as a potential risk factor in CV risk factor studies.[51,52]

AHI was the most frequent significant predictor of outcomes of interest. Other predictors found to be significant have been recommended in previous reviews for inclusion in any risk prediction score for CVD: age, sex, BP, BMI, cholesterol level, smoking status, diabetes status and CV disease at baseline.[53,54] Although these traditional CV risk factors were included in statistical models in the majority of studies, they were statistically significant in fewer than half. It is difficult to draw conclusions as to the importance of these predictors in OSA since analyses included different combinations and definitions of predictors, as well as a variety of primary and subgroup analyses.

The majority of studies focused on the relationship between AHI and our outcomes of interest, and found that a higher AHI at baseline was associated with a higher risk. However, different thresholds of AHI were reported as predictive. Although the SHHS cohort[55] reported that differing definitions of hypopnea (in particular different desaturation criteria, decrease in $SaO_2 \geq 4\%$ or less) affected the association between OSA and CVD, we did not confirm this effect in other reviewed studies. Among eight studies that did

not find an association between OSA and outcomes of interest, four studies used a definition of a decrease in SaO_2 more than 4%, two a decrease more than 3% and two did not clarify. Almost none of the studies reported the exact settings of the oximeters used to quantify dips in SaO_2. Not only were different desaturation criteria used to define hypopneas but also highly variable changes in oronasal flow (30%, 50% and 70%).

Although AHI reflects the number of arousals and level of SaO_2, it may not accurately reflect the most relevant pathophysiological aspects of OSA contributing to long-term CV consequences.[9,56] Combinations of PSG indices, such as frequency and duration of apneas, as well as frequency and degree of dips in SaO_2 may better represent the overall CV burden of OSA. However, few studies examined PSG indexes other than AHI as predictors of long-term consequences of OSA. Furthermore, other variables which are not routinely measured during PSG, but which are known to be disturbed during OSA, such as negative intrathoracic pressure swings, might be important.[9]

There is some evidence (three studies of high quality) that the effect of AHI on risk of development of all-cause mortality and CV events including stroke is attenuated by female gender. The effects of age and sleepiness on the strength of association between OSA related variables (AHI, SaO_2) and outcomes of interest remain uncertain.

There are a number of possible explanations for the seemingly lesser effect of OSA on the development of CV disease in women. First, women are underrepresented in clinical studies, have a lower prevalence and severity of OSA, and a lower CV event rate, all of which may contribute to an inability to detect an association due to lack of statistical power. Second, although the lifetime risk of CV disease in women approaches that of men, women often present later in life and studies examining five or even ten year risk may underestimate the burden of disease which is often subclinical in women earlier in life.[57] Finally, it is possible that women differ from men in their underlying physiologic pathway to CV disease and are truly less vulnerable to the disturbances of OSA. Further study is required to determine whether this sex effect is real and if it is, to develop a therapeutic strategy for women with OSA.

Some studies reported that, in comparison to their age-matched population, younger people with OSA had a higher risk of mortality than older people.[12,37,42] However, this “younger” age group was defined differently in different studies, for example, less than 50 years old,[37] 30–69 years old[42] or 40–70 years old.[12] Possible explanations for the observed lower mortality rate in older individuals include: i) referral bias, by which healthier elderly people were referred to a sleep laboratory; ii) a survivor bias, by which elderly people remaining alive tend to be healthier than those who have already died; iii) the beneficial effect of treatment on patient survival, not accounted for in some studies; or iv) apnea-related activation of cardioprotective adaptive pathways through mild chronic intermittent hypoxia.[39,58,59] It is also possible that for the samples included in this review, CV risk factors developed later in life for older patients than for younger patients, resulting in a higher relative mortality rate in the younger group compared to the older one. If confirmed by further research, one proposed response to these findings is a more aggressive diagnostic and therapeutic strategy for younger and middle-aged subjects with OSA.[23]

Limitations

We acknowledge heterogeneity in the primary studies, which demonstrate a great deal of variation in the populations studied and definitions of OSA, AHI and the composite CV outcome.

The main concern regarding the community based studies, which were found to be “high quality”, is that severe OSA is underrepresented, with 341 cases in 6294 subjects in the SHHS[32] and 63 in 1522 in the WSCS.[16] Similarly, none of the studies distinguished patients with OSA from those with obesity-hypoventilation syndrome (OHS) or hypercapnia, an increasingly common subgroup of patients with sleep disordered breathing that overlaps strongly with OSA. It is likely that whatever CV risk is attributable to OSA is still greater in patients with OHS,[60] but this remains a gap in our knowledge. Additionally, most (>70%) patients with severe or severe-moderate OSA in these two cohorts were men. These small numbers limit the precision of estimates of risk for severe OSA, especially for women. Also, higher lifetime risks of death from CVD or coronary heart disease or of nonfatal MI were reported among men than among women.[48] Thus, the power to detect clinically important effects in women was low.

In addition, despite all-cause mortality being the most robust and reliable outcome,[61] some causes of death may have no pathogenic link to OSA. Interpretation of the composite CV outcome is muddied by the following issues: i) the individual components vary by clinical importance; ii) the event rates or relative risk reductions may vary among the components; iii) the greater the number of components, the more complex it is to carefully assess the composite outcome in the primary studies.[62]

Most studies focused on AHI or an equivalent measure of OSA; the strength and significance of associations with other factors (e.g., other PSG indexes or clinical symptoms) were often not reported. Our assumption was that in the case where statistical significance or the magnitude of an association was not reported, despite the inclusion of a variable in a statistical model, the association was not statistically significant. Thus, the roles of other factors could be underestimated in this review.

Also the possibility exists that the associations between OSA and the outcomes of interest can be attenuated due to “overcontrolled” models. For example, since there is a possible causal relationship between OSA and HTN,[23] including HTN in a model can attenuate the association between OSA and CVD because HTN is in the causal pathway. Similarly, including obesity in a model could attenuate the relationship between OSA and diabetes. The choice of an inappropriate control group could also have caused attenuation of associations; for example, non-apneic subjects with snoring may still be at elevated risk of CV events due to increased swings in intrathoracic pressure.[63]

The focus of this review was the natural history of patients diagnosed with OSA, not the effect of treatment. A potential limitation is that patients who were treated and who were adherent to treatment also exhibited other beneficial health behaviours.[64] This could lead to residual confounding. One of the few long-term clinically-based studies comparing CV outcomes in patients on or off treatment[14] was an observational cohort study showing a strong relationship between untreated OSA and cardiovascular risk, but it has been criticized on the grounds that non-adherence to CPAP is possibly correlated with other unhealthy behaviours. However, a follow-up study from the same group[65] did not find any correlation between CPAP use and adherence to three cardiac medications (antihypertensives, statins, and antiplatelets) over a two year period, suggesting that this confounding is possibly less important than had been surmised. Nonetheless, there is a strong need for large, prospective, randomized controlled trials to put this issue of possible confounding to rest.

Finally, the inclusion of only English language articles could affect the generalizability of our findings.[66]

Conclusion

Evidence exists in men for a relationship between OSA and all-cause mortality and a composite CV outcome. Associations between OSA and other outcomes remain uncertain. Among OSA-

specific markers, only AHI was a consistent predictor. Other consistent predictors were traditional CV risk factors. Research is required to identify effect modifiers and the predictive ability of various AHI threshold values and hypopnea definitions. An enhanced set of OSA-specific predictors will allow better risk stratification to guide OSA treatment. Future studies should consider a common set of predictors and definitions of OSA, AHI (and within that hypopneas) and outcomes to decrease the clinical heterogeneity.

Practice points

A systematic review of the prognostic value of risk factors for adverse long-term outcomes of untreated obstructive sleep apnea (OSA) revealed the following:

1. Evidence exists in men for a relationship between OSA and both all-cause mortality and a composite cardio-vascular outcome (composite of cardio-vascular events, e.g., myocardial infarction, stroke, hospitalization due to revascularization procedures and heart failure).
2. Associations between OSA and other clinically important outcomes (diabetes and depression, separate components of composite cardio-vascular outcome) remain uncertain.
3. Among OSA-specific markers, only the apnea–hypopnea index was a consistent predictor. Other consistent predictors were traditional cardio-vascular risk factors (age, sex, blood pressure, history of cardio-vascular comorbidities and diabetes at baseline).

Research agenda

1. Further research is required to identify:
   - Effect modifiers (e.g., effect of sex, age, daytime sleepiness and body mass index on the predictive ability of the apnea–hypopnea index);
   - The predictive ability of various apnea–hypopnea index threshold values;
   - Whether patients with pre-existing cardiovascular disease or traditional cardiovascular risk factors are at higher risk for the effects of obstructive sleep apnea (OSA) and might need to be treated at lower thresholds of the apnea–hypopnea index;
   - The effect of different definitions of hypopnea on the accuracy of the apnea–hypopnea index in predicting cardiovascular disease.
2. Ultimately, the goal should be development of a comprehensive, enhanced set of demographic, clinical and polysomnographic predictors that would allow better risk stratification to guide OSA treatment, since OSA is very common and expensive to treat on a population level.

Conflict of interest statement

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Appendix A. Inclusion criteria

Types of participants: The target population was adult patients with a diagnosis of OSA made by polysomnographic (PSG) recording, either in a sleep laboratory or using portable (home) monitoring, on the basis of the apnea–hypopnea index (AHI) or a validated equivalent. Minimum respiratory channel and monitoring of blood oxygenation needed to be included in recording for a study to be eligible.

The baseline sample should be adequately described for the key characteristics: age, gender, severity of OSA, comorbidities at baseline.

Studies with more than 50% of participants with i) previous CV events (MI, stroke, severe heart failure (HF) that required hospitalization, revascularization procedure) or ii) other severe neurological or psychiatric diseases or iii) pregnant women, were excluded. Those that did not include an untreated OSA group were also excluded.

Potential predictors: No studies were excluded based on the choice of predictors they considered. All available clinical information (including information from the history, examination, blood, imaging and other investigations) and PSG indexes were treated as predictors. Only predictors that were statistically significantly associated with outcomes of interest in at least one study were reported. Factors associated with outcomes of interest were collated into four domains: patient demographic characteristics, medical history, physical exam, and disease (OSA) characteristics (clinical symptoms, PSG indexes, treatment options).

The effectiveness of OSA treatment on adverse long-term consequences of OSA was not a focus of this review.

Outcomes: The following serious adverse long term consequences of OSA, documented or self-reported by participants, were considered: CV events, both non-fatal (e.g., coronary artery disease (CAD), MI, stroke, HF, revascularization procedures) and fatal; all-cause mortality; diabetes; and depression.

Follow-up: Minimum one year of follow-up was considered for inclusion.

Appendix B. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.smrv.2013.01.003.

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